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SECOND REVIEW OF SOME OF THE RECENT ADVANCES IN TROPICAL MEDICINE.

LEISHMANIASIS

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SECOND REVIEW

OF SOME OF THE

RECENT ADVANCES IN TROPICAL MEDICINE

HYGIENE AND TROPICAL VETERINARY SCIENCE

BEING A SUPPLEMENT TO THE

FOURTH REPORT

OF THE

WELLCOME TROPICAL RESEARCH LABORATORIES

AT THE

GORDON MEMORIAL COLLEGE
KHARTOUM

BY

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Insects— *continued*

A good remedy for the pain of insect bites is stated to be a mixture made by dissolving 30 or 40 grains of iodine crystals in one ounce of saponated petroleum (Moloney). It is said to remove the pain of wasp or mosquito bite "like magic."

Additional Notes

Wellman [1] has an interesting lecture on insects and human disease in the Tropics. Although it chiefly refers to conditions met with in Angola it forms a good contribution to the literature. He says that craw-craw is really due to scabies. Myriapods are mentioned, both centipedes and millipedes. The former bite severely, the latter excrete a poisonous secretion, probably from the *Foramina repugnatoria* at the sides of their segments. He has something to say about the *Orthoptera*, mentioning especially *Dacnodes wellmani*, a new giant earwig, which can draw a large drop of blood with its pincers, and may introduce septic matter into the wound it produces. He also notes that possibly a tape-worm (*Davainea*) may be disseminated by cockroaches. He again describes *Phonergates bicoloripes*, the bug that preys upon *O. moubata*, and mentions other groups of bugs, notably species from South America, which are said to suck human blood. The remarks on flies and fleas do not call for notice here, but the author deals also with beetles. The larvæ of *Blaps mortisaga* are often found as pseudo-parasites in man, and Daniels found a coleopterous larva in an abscess case in Demerara. Other beetles are said to be intermediate hosts of tape-worms. There are beetles with poisoned spines (*Drilus and Tetralobus*), and bushmen prepare a deadly arrow poison from the grubs of a chrysomelid beetle (*Diamphidia locusta*). Some large African carabidæ eject with great force a strong-smelling liquid from the posterior part of the abdomen, which, if it reaches the eye, gives rise to a severe irritative conjunctivitis. Urticaria due to Lepidoptera claims attention; moths are mentioned as the secondary hosts of cestodes, and as parasites on mammals; and, following Williamson, the rôle of ants as possibly spreading anthrax receives consideration.

Maxwell-Lefroy [2] supplements Howlett's note (*loc. cit.*). He says :—

> We use teak boxes of a standard size well varnished within; when the varnish is dry, a piece of cork carpet cut to fit the box and previously enamelled white above, is laid ready to hand, a mixture of paraffin wax (melting point 136° F.) 80 per cent. and flake naphthalene 20 per cent. is kept melted and a small quantity is run into the box, the cork carpet is at once put in and rolled down on the melted mixture which sets and holds it; more of the liquid is then run in, sufficient to cover the cork completely: this sets with an even smooth surface (the box being on a perfectly horizontal surface), and the box is ready when cold. This method has not only been tried, but we have nearly 2000 boxes in use, and are replacing all our papered boxes.

Such boxes are too heavy if one is moving about, and for that a lighter paraffined box is recommended. The paraffined cork requires no poisoning, keeps white and does not harbour insects.

Stevenson [3] mentions a method for killing bed-bugs which has been successfully used in sleeping carriages at the Cape of Good Hope. It consists in the use of potassium cyanide 1 ounce to 100 cubic feet, with an exposure time of two hours. It not only kills the majority of the bugs present, but prevents eggs from hatching out.

Leishmaniasis. Under this heading oriental sore is not included. We consider only infantile kala-azar, and the ordinary disease of that name. The most notable discovery regarding both these forms, if indeed they are separate forms of the disease, is the recognition of their wide distribution. Already well-nigh every country of the Mediterranean littoral has been found to harbour cases of the infantile form, while, in not a few, Leishmania have also been found in adults. Other countries also, such as Portugal, not hitherto known to be infected, have been proved to be so, at least to some extent. Hence at the present time there is no more interesting and important disease than that which gives this section its title. In the first place we consider a paper dealing with the infantile form. Nicolle's work was cited in our first Review. In a paper [4] which escaped attention he describes the successful cultivation of Leishman bodies obtained from the spleens of three infantile cases. He employed blood-salt-agar, and gives its formula and the technique for its preparation. At 22° C. culture forms did not appear till about the seventh day, but were abundant by the twelfth. The parasites

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[1] Wellman, C. (1910), "Diseases in the Tropics.—Lecture I. Insects and Human Disease in the Tropics." *Collected Papers American Society of Tropical Medicine.*

[2] Maxwell-Lefroy, H. (June, 1911), "Note on Entomological Boxes." *Parasitology.*

[3] Stevenson, W. W. H. (June, 1911), "Bugs in Railway Carriages." *Indian Medical Gazette.*

[4] Nicolle, C. (1908), "Culture des corps de Leishman isolés de la rate dans trois cas d'anémie splénique infantile." *Bull. Soc. Path. Exot.*

were still living and motile after three months, and presented all the familiar cultural forms of *Leishmania donovani*. Subculture was easy. He gives a method for staining these cultural forms by Giemsa. In a later paper [1] the same author signalises the discovery of *L. infantum* in the peripheral blood where, however, it is not easy to find. In the infant he does not think liver puncture can replace splenic puncture, as the results are inconstant. It is, however, excellent for following out the development of the parasite and the progress of the infection in experimental animals such as the dog and the monkey. In this paper he mentions the spontaneous leishmaniasis of dogs in Tunis, and reaffirms his belief as to the canine origin of infantile kala-azar. One need not cite all the scattered earlier papers on the subject, for Nicolle [2] has gathered all the facts collected down to the middle of 1909 into a couple of excellent papers illustrated by temperature charts and coloured plates. He gives a full bibliography, and summarises in twelve conclusions, some of which we note :— Leishmaniasis—*continued*

(1) The malady is confined to young children, and usually makes its appearance in the course of the second year of life, but it may develop earlier or later.

(2) The symptoms are characteristic, and are extreme pallor, marasmus, considerable splenomegaly, a somewhat less enlargement of the liver, fleeting and painless œdemas, a very irregular temperature capable of exhibiting several "maxima" on the same day, a notable quickening of the pulse rate, digestive troubles and an increase of the mononuclear elements of the blood. Hæmophilia, gingivitis and purpura are frequently complications. The duration of the illness is very long. Death is the rule, but spontaneous cure may apparently occur.

(3) Quinine has no effect upon the fever.

(5) Post mortem, in addition to the splenic and hepatic hypertrophies, the bone-marrow is found to be red in colour.

(6) The condition only differs from true kala-azar in the age of the patients.

(7) It is allied to the splenic anæmias of infancy, and is apt to be confounded with them.

(8) On blood-salt-agar the cultural forms take the herpetomonas type.

(9) Dogs and monkeys can be infected. Other animals seem to be refractory. In the dog the disease is often benign so far as symptoms go, but terminates fatally. The monkey infection is more like the human. The dog infection is not transferable from mother to fœtus.

(10) Small doses of cultures are innocuous to the dog, but large and repeated doses, as in Novy's kala-azar experiments, produce infection.

(11) The disease is a natural infection of the dog transmissible to the child. The absence of clinical symptoms in the animal makes it difficult of recognition.

(12) The transmitting agent requires discovery.

With this valuable list as a basis let us explore further developments. Novy [3] has succeeded in inoculating dogs with smaller doses of cultures, and recommends blood culture as a means of diagnosis in doubtful cases. In addition to the nucleus and blepharoplast, he finds the parasite possesses a rhizoplast which he illustrates rather feebly by photographs. This proves the parasite to be a flagellate. The rhizoplast is always perpendicular to the blepharoplast, and is a spherical body, the root, indeed, of a flagellum.

A considerable number of papers will be found in the *Archives of the Tunisian Pasteur Institute* for 1909, but as their contents are repeated in later papers, or as they deal with unsuccessful attempts at treatment with arsenophenylglycin, etc., the mere reference must suffice. One paper only will be mentioned, *i.e.* that wherein Nicolle and Manceaux [4] show that the virus diminishes in activity by passage through the monkey. The indefatigable Nicolle [5] again summarises some of the later work published in the above-mentioned *Archives*. A dog inoculated experimentally 18 months before succumbed to the disease, which was entirely latent, the temperature being normal for 16 months. The parasite was found in blister serum taken from this dog, a fact indicating a possible means of diagnosis in the human subject. The mononuclear leucocytes were infected. The above-mentioned monkeys recovered after injection with the weakened virus. Dogs, on the contrary, died after severe attacks.

Inoculation with *L. tropica* appears to protect monkeys, wholly or partly, against infection with *L. infantum*. Subcutaneous inoculation with a weakened virus in a monkey produced a local lesion, but no general infection. The local lesion did not resemble oriental sore. Comte

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[1] Nicolle, C. (1908), "Quelques faits nouveaux relatifs au Kala-azar Infantile." *Bull. Soc. Path. Exot.*

[2] *Idem* (May 25, and June 25, 1909), "Le Kala-azar Infantile." *Ann. de l'Inst. Past.*

[3] Novy, F. G. (1909), "Sur Leishmania infantum." *Bull. Soc. Path. Exot.*

[4] Nicolle, C., and Manceaux, L. (1909), "Résistance du singe au virus du kala-azar après passage de ce virus par le singe." *Archiv. de l'Inst. Past. de Tunis*, No. IV., p. 188.

[5] Nicolle, C. (1909), "Quelques données nouvelles relatives au Kala-azar Infantile." *Bull. Soc. Path. Exot.*

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continued

and Manceaux assisted Nicolle in this work. Laveran and Pettit [1] found that both in dogs and monkeys the infection might be either very slight or latent, and only recognisable by cultural methods, for both liver puncture and the examination of the bone-marrow during life might give negative results. Aspland [2] has found infantile kala-azar common in Peking, and believes it may exist throughout North China. In Peking the features of the disease are—

(1) Age rarely under two years, and never over ten.

(2) The spleen is always much enlarged, in later stages filling the pelvis.

(3) Diarrhœa in the later stages, constant and severe.

(4) Great debility generally, but not pronounced until the cancrum oris has set in.

(5) "Cancrum oris." The condition does not really affect the cheek, but begins at the root of the upper or lower central incisors, the teeth dropping out in a week or so, leaving a black slough. The author favours a syphilitic origin of the disease.

(6) The disease is always fatal.

(7) As regards fever, no data were obtainable.

He mentions that in one case in Tientsin, Leishman bodies were found in the peripheral blood.

Cannata [3] has examined the blood in seven cases of the disease. The formula varies very much, not only in different cases, but in the same case at different times. It is therefore unlikely to be of value for diagnosis. The presence of myelocytes was noted. Once more we find Nicolle [4] presenting new discoveries regarding the disease in Tunis. Amongst other points we note a case apparently cured, one successful case of diagnosis from blister fluid, no evidence of a lessening in virulence of the virus by passage through dogs, a great variation in its action for different animals of any one batch even when the same doses and the same method of administration are employed. It is specially noteworthy that the injection of a large number of parasites does not necessarily mean a severe infection. A first attack of the experimental disease can, as shown in cases apparently cured for some time, confer complete immunity on dog and monkey. In an animal incompletely cured or only recently recovered, however, a second inoculation proves fatal.

Removal of the spleen in an infected dog does not influence the course of the disease. Subcutaneous injection in the dog and monkey may be followed by a local reaction as well as a general infection. The former is not like that which follows subcutaneous inoculation with *L. tropica*. The site of selection for liver puncture in the dog is the tenth right intercostal space one or two fingers-breadth from the costo-vertebral joints. A steel needle, free from all rust and slightly longer and stronger than that used in the case of children, is indicated. These are the results of work performed by Nicolle and his colleagues, *i.e.* Cortese, Lévy, Triolo, Conor, Comte and Manceaux, and the details of which will be found in the three numbers of the *Archives of the Tunis Pasteur Institute* for 1909.

A number of Italian and other papers will be found reviewed in the *Bulletin of the Pasteur Institute* for August 15, 1910. We note the following: Basile [5] has, in Sicily, confirmed Nicolle's work as regards the presence of spontaneous Leishmaniasis in the dog. One of the villages where the discovery was made was where Gabbi [6] found infantile cases. The work of Jemma [7] and other observers is also cited. They succeeded in inoculating dogs both intraperitoneally and intravenously. The cases found by Alvarez [8] and his colleagues at Lisbon also receive mention. So does the work of Critien [9] in Malta. He found ten cases there. We only give here a selection from the numerous papers reviewed, but some of these

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[1] Laveran, A., and Pettit, A. (1909), "Infections expérimentales légères au latentes du singe et du chien par le Kala-azar tunisien." *Bull. Soc. Path. Exot.*

[2] Aspland, W. H. G. (January 15, 1910), "Is Ponos Kala-azar?" *British Medical Journal.*

[3] Cannata, S. (May, 1910), "Recherche ematologiche nell' anemia splenien infantile de' parassiti di Leishmann." *La Pediatria.*

[4] Nicolle, C. (July 13, 1910), "Quelques données nouvelles relatives au Kala-azar Infantile." *Bull. Soc. Path. Exot.*

[5] Basile, C. (1910), "Alcune osservazioni sulla presenza di Leishmania nei cani." *Rend. d. Accad. dei Lincei*, Vol. XIX., No. 3.

[6] Gabbi, U. (1909), "Facolai endemia della varietà febrile l'anemia splenica infetiva dei bambini." *Policlino.*

[7] Jemma, R., Cristina, G., and Cannata, S. (1910), "Infezione sperimentale da 'Leishmania infantum' nei cani." *La Pediatria.* See also *Cent. f. Bakt.*, I. Orig., December 17, 1910, Vol. LVII., No. 1.

[8] Alvarez, D. (March 20, 1910), "Um caso de Kala-azar infantil em Lisboa." *Med. contemp.*

[9] Critien, A. (1910), "Kala-azar infantile à Malte." *Archiv. de l'Inst. Past. Tunis*, No. 2.

Leishmaniasis—*continued*

authors have carried out later work of interest and value which we now proceed to discuss. Thus Basile [1] describes two different forms of natural infection in dogs, the acute and the chronic. He thinks that the former, which affects young dogs and lasts from 3 to 4 months, plays the more important part in the spread of the disease. This author was able to infect three young dogs by keeping them beside cases of infantile kala-azar, and believes that the flea (*Pulex serraticeps*, and possibly also *P. irritans*) is the most likely vector. Quite recently Critien,[2] in the case of a child aged 3 years, found the parasites in smears from mucous flakes excreted with the fæces. It is evident that if this observation is confirmed in other cases it may possess much significance.

Cristina and Cannata [3] have a paper on the morphology and cultural characteristics of *L. infantum*, in which they describe involution and other forms. A few illustrations would have been helpful. The Sergents [4] announce the presence of the parasite in dogs in Algiers. Commenting on their figures, Nicolle [5] points out that protozoal infections are more common in the summer, when they made their examinations, than in the spring, when he made his researches on dogs. The disease has recently been found in Tripoli, and Jérusalemy [6] has now confirmed Aspland's view (*loc. cit.*) as to its occurrence in China.

Ponos has been mentioned in the references, and there has been some discussion as to whether this disease of the Greek Archipelago is, or is not, kala-azar. Williamson [7] was the first to advance the former view, and it appears to be correct, to judge by Galle's [8] recent discovery of *Leishmania* in a case of "ponos" at Spetsai. Leaving aside for the present papers on the efforts at treatment in the infantile form, we turn to kala-azar proper, the disease affecting both adults and children, and due to *L. donovani*. Patton [9] believes that it should be named *Herpetomonas donovani*, regards it as allied to *H. muscæ domesticæ*, and even more closely to *H. lygæi*. (*See also* paper by Archibald in the Fourth Report of these Laboratories, Vol. A.) He suggests the term herpetomoniases for the group of diseases now classed under leishmaniases. He was unable to transmit the disease to dogs. In a previous paper [10] he had given an account of his few experiments with dogs, and had stated that in Madras there was no evidence that dogs play any part in the spread of kala-azar. Speaking of the genus *Herpetomonas*, he says :—

> In their pre-flagellate stages they are round or oval bodies of varying size, and contain two characteristic chromatic bodies, the nucleus and blepharoplast. In this stage they multiply by simple longitudinal fission or by multiple segmentation, and are found in the midguts of their insect hosts, except in the case of the three human parasites. I have been able to show that this stage in a known species occurring in *Culex* mosquitoes is exactly similar to that of the human parasites. The flagellate stage is characterised by the formation of a *single* flagellum, and the multiplication of the resulting flagellates by equal or unequal longitudinal division. The adult forms are long, spindle-shaped organisms, with a single flagellum, but no undulating membrane. This stage occurs in the mid- and hind-gut of their hosts, but in the case of *Herpetomonas donovani* it takes place naturally in *Cimex rotundatus*. The post-flagellate stage is characterised by the massing together of the flagellates in the midgut, their shortening and rounding up; the resulting cysts are passed out in the fæces and are accidentally sucked up by fresh hosts. It is not known yet whether *H. donovani* undergoes this stage in the bed-bug.
>
> It is important to remember that many of these *Herpetomonads* are indistinguishable in their *pre-flagellate stages*, and therefore if this stage alone is studied two distinct species may be classed as one. Further, I wish to point out here that a partial study of the stages of these flagellates is very apt to lead to confusion, so that what are true *Herpetomonads* may quite easily be mistaken for *Crithidia* or young *Trypanosomes*. A reference to recent literature will show that this has actually occurred in more than one instance.

Donovan [11] expressed himself as dissatisfied with Patton's bed-bug theory, and suggested

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[1] Basile, C. (1910), "Sulla Leishmaniosi del cane e sull'ospite intermedio del Kala-azar infantile." *Rend. d. Accad. dei Lincei*, Vol. XIX., No. 5.

[2] Critien, A. (January 28, 1911), "Kala-azar in Malta." *British Medical Journal.*

[3] Cristina, G., and Cannata, S. (September 6, 1910), "Über die morphologischen und kulturellen Eigenschaften des Parasiten der infantilen Milzanämie." *Cent. f. Bakt.*, I. Orig., Vol. LV., No. 6.

[4] Sergent, Ed. and Et. (October 12, 1910), "Existence de la leishmaniose chez les chiens d'Alger." *Bull. Soc. Path. Exot.*

[5] Nicolle, C. (January 11, 1911), "A propos de la leishmaniose canine en Afrique Mineure." *Ibid.*

[6] Jérusalemy (May, 1910), "Kala-azar infantile en Chine." *Rev. de Méd. et d'Hyg. Trop.*

[7] Williamson, G. A. (August 16, 1909), "Is Ponos Kala-azar?" *Journal of Tropical Medicine and Hygiene.*

[8] Galle, (January 2, 1911), "Is Ponos Kala-azar?" Professor Galle's Discovery, Article in *Journal of Tropical Medicine and Hygiene.*

[9] Patton, W. S. (January 30, 1909), "The Parasite of Kala-azar and Allied Organisms." *Lancet.*

[10] *Idem* (December, 1908), "Inoculation of Dogs with the Parasite of Kala-azar (*Herpetomonas* [Leishmania] *donovani*), with some Remarks on the Genus Herpetomonas." *Parasitology*, Vol. I.

[11] Donovan, C. (1909), "Kala-azar in Madras." *Transactions Bombay Medical Congress.*

a reduviid bug, *Connorrhinus rubrofasciatus*, as a possible carrier. No experimental proof has been advanced that this is the case, but it is interesting to note that the human *Trypanosoma cruzi* of Chagas undergoes development in a bug of this genus. Of more importance are some other notes by Donovan. He has abandoned splenic puncture as a means of diagnosis, and relies on the examination of films of peripheral blood prepared in a special manner. Here is the technique :—

A finger of the patient is taken, the tip washed with water and then dried with a towel, the finger is compressed below the pulp for half a minute so as to allow as many leucocytes as possible to exude in the drop of blood obtained by the prick of a new pin, one not used before. A needle's prick does not give enough blood, and the employment of a surgical needle is barbarous. A small drop of blood, about the size of a large pin's head, is taken up by a slide near its end and a smear made of it by another slide passed slantwise over it.

The main object is to have the smear end in a straight edge at the finish. All that is necessary is to examine, of course after fixing and staining the film, this edge; here everything of importance in the smear is located, the leucocytes and any Leishmania that may be present in them; in ten minutes the whole of the contents of the drop of blood are ascertained. Some training is necessary to procure perfect slides of this nature. The slide with which the smear is made should have a perfectly smooth-ground edge to obviate "tailing" at the finished margin. It is by neglect of making smears of this kind that success does not attend the endeavours of other observers in detecting Leishmania in the peripheral blood.

In a later paper [1] this author mentions that the *Connorrhinus* sucks human blood, and describes negative experiments in dog inoculation.

He has tried quinine, fuchsine, and other methods of treatment, but change of air appeared to be the only curative agent known so far.

Treatment with hetol, 0·1 c.c. of a 1 per cent. solution by intravenous injection, the dosage being gradually increased, was carried out by Harrison [2] in an Indian case, and was followed by some improvement, especially as regards the temperature and the blood condition. Soamin and exposure of the spleen to X-rays produced no benefit. McKaig [3] reported a case of apparent cure after atoxyl, in doses varying from 6 to 12 grains daily. Laveran and Pettit [4] inoculated mice and a guinea-pig intraperitoneally, and some rats in the liver, with emulsions of organs rich in *L. donovani*. (As the strain was Tunisian it would seem to have been *L. infantum*, unless one is agreed that the species are identical.) The animals remained perfectly well, but intra-cellular parasites were found for some time in the peritoneal exudate which also yielded cultures of flagellates on the Novy-Nicolle medium. In one instance a mouse inoculated subcutaneously showed five days afterwards a very few Leishmania in its peritoneal cavity. Otherwise the parasites did not appear capable of traversing the peritoneum. Nicolle [5] has a short paper on the technique of spleen puncture. He advises a fine needle, and points out that one does not wish to see any blood appear in the barrel of the attached syringe. There is usually enough fluid in the lumen of the needle to make all the smears required. Moreover, if cultures are required, it is to be remembered that any blood will have an inhibitive effect on growth.

Platinum-iridium needles and old needles, especially if the least rusty, should never be used. In short, new steel needles of fine calibre are indicated. The syringe must be dry, and for this purpose may be passed through a Bunsen flame or put in a hot oven. Day and Ferguson [6] have described a form of splenomegaly with hepatic cirrhosis which is endemic in Egypt. They have never found Leishmania present, but have noted marked changes in the bone-marrow. The cause of this curious condition is unknown, but they compare it with kala-azar, saying :—

Kala-azar, while closely resembling the condition which we have described in certain respects, differs from it in others. Thus the febrile onset, chronic course, presence of intestinal symptoms, the aspect of the patient in the advanced stages, the condition of the blood, bone-marrow and spleen, are very closely similar in both affections. Kala-azar, however, in the following particulars, apart from certain clinical features, differs from the condition to which we have called attention.

(1) The presence of a crusted papular eruption or of ulcers on the limbs, containing the parasite.

(2) The presence of intestinal ulcers, chiefly in the colon, also containing the parasite in small numbers.

(3) The tendency to noma and local areas of gangrene, as well as to internal hæmorrhages.

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[1] Donovan, C. (November 20, 1909), "Kala-azar in Madras, especially with regard to its connection with the dog and the bug (connorrhinus)." *Lancet.*

[2] Harrison, L. W. (January, 1909), "A Case of Kala-azar." *Journal Royal Army Medical Corps.*

[3] McKaig, A. (December, 1908), "Atoxyl in the Treatment of Kala-azar." *Edinburgh Medical Journal.*

[4] Laveran, A., and Pettit, A. (July 3, 1909), "Infections légères du rat et de la souris par la Leishmania Donovani. Idem du cobaye." *C. R. Soc. Biol.*

[5] Nicolle, C. (1909), "Sur la technique de la ponction de la rate." *Bull. Soc. Path. Exot.*

[6] Day, H. B., and Ferguson, A. R. (1909), "An Account of a form of Splenomegaly, with Hepatic Cirrhosis Endemic in Egypt." *Annals of Tropical Medicine and Parasitology*, Vol. III., No. 3.

Leishmaniasis—*continued*

(4) The condition of the liver. In sporadic kala-azar, according to Rogers' observations, the liver showed marked cirrhotic changes in four out of forty-eight cases examined post mortem, while slight degrees of fibrosis were observed in a certain additional number. In the condition we are describing, however, hepatic changes in various degrees form an integral part of the malady at different stages, and are constantly met with. Again, the type of cirrhosis met with is portal in character and not intralobular, as described by Rogers for kala-azar. And lastly, "the persistence of the parasites in the advanced cirrhotic stage of the organ," as noted by Rogers in kala-azar, is a feature which stamps a distinctive character on the liver in this affection.

As already noted, Gabbi (*loc. cit.*) found the disease in Sicily. He has discovered it in adults as well as in children, and true kala-azar has also been found to exist in China, as reported by Bassett-Smith.[1] The upper part of the Yangtse Valley is evidently an endemic centre.

Harrison and Cumming[2] reported two cases in which treatment by arylarsonates failed to avert fatal issues. Atoxyl, soamin and arsacetin were all used without benefit. Archibald[3] investigated the alkalinity of the blood serum of four cases in the Sudan, and concluded that—

It is evident that the alkalinity of the blood in these four cases of undoubted kala-azar was diminished, and it is worth remembering that Rogers, Leishman, Statham, and other observers found that the ideal culture media for successful cultivation of the Leishman body is an acid one.

If, then, the alkalinity of the blood serum in cases of kala-azar be diminished, it is conceivable that the blood and tissues present a more favourable medium for the Leishman parasite than is usually the case; and, in order to obviate this, it would not seem unreasonable, whatever specific line of treatment be adopted, that drugs should be administered which tend to increase the alkalinity of the blood.

Of the above cases, only one was subjected to an alkaline treatment by calcium lactate, and unfortunately the disease was so far advanced in this instance that the drug had scarcely a fair trial.

A specific drug for the successful treatment of Leishmaniosis has not yet been found. Quinine and various arsenical preparations have not given satisfactory results up to the present, and hence the record of these four cases points to the advisability of employing such remedies as would increase the alkalinity of the blood.

Further, the alkaline reaction obtained in testing the serum of kala-azar cases may be of service in assisting the diagnosis in early cases where splenic enlargement is not marked.

Laveran and Pettit[4] recommend the use of a fluid medium for cultivating *L. donovani*, especially when a large growth is required for the purposes of experimental inoculation. The following is the formula they employ :—

Peptone (chapoteau)	2 grammes	1 Volume
Sod. chlorid.	6 grammes	
Water	900 grammes	
Defibrinated rabbit's blood		1 Volume

The peptone-salt solution is prepared separately and then the blood is added to it. Cubical flasks or Roux's bottles laid flat are used, so that the liquid may have as large a surface area as possible, because the parasites do not develop in the depths of the medium. The medium must be fluid, not sticky, and should present the aspect of laked blood. In such a medium the Leishmania agglomerations show as numerous white particles plainly visible to the naked eye. An important and well illustrated paper on kala-azar in the Sudan is that by Bousfield,[5] a résumé of which appears in the Fourth Report of these Laboratories, together with later papers by Douglas Thomson and Marshall.[6] Bousfield did not find the parasite in two dogs which he examined, and his paper is more of local than general interest. At the same time he gives a good clinical account of the disease as met with in certain parts of the Anglo-Egyptian Sudan, and deals with preventive measures, such as the avoidance of native bedsteads. Thomson extended Bousfield's clinical studies, while Marshall has worked at the pathological aspects of the disease in the Sudan. Their joint conclusions are as follows :—

(1) Kala-azar in Sennar Province affects, for the most part, children whose average age is about 12 years. This does not appear to hold in the neighbouring Province of Kassala, where adults are commonly affected.

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[1] Bassett-Smith, P. W. (December 4, 1909), "Kala-azar in the Far East." *British Medical Journal.*

[2] Harrison, W. S., and Cumming, C. C. (February, 1910), "Two cases of Kala-azar treated by the Arylarsonates." *Journal Royal Army Medical Corps.*

[3] Archibald, R. G. (June, 1909), "The Alkalinity of the Blood Serum in Kala-azar." *Ibid.* See also *Fourth Report, Wellcome Tropical Research Laboratories*, Vol. A.

[4] Laveran, A., and Pettit, A. (April 13, 1910), "Sur les cultures de 'Leishmania donovani' en milieu liquide." *Bull. Soc. Path. Exot.*

[5] Bousfield, L. (August and September, 1910), "A Tour of Investigation as to the prevalence of Kala-azar in Kassala and Blue Nile Districts, Sudan, from January 12 to May 16, 1909." *Journal Royal Army Medical Corps.*

[6] Thomson, D. S. B., and Marshall, W. E. (1911), "Kala-azar Commission to investigate the prevalence and cause of the disease in the Eastern Sudan." General and Pathological Reports. *Fourth Report, Wellcome Tropical Research Laboratories*, Vol. A.

Leishmaniasis— *continued*

(2) The disease runs an acute course, and chronic cases were not met with.

(3) The disease is not invariably fatal, cases of recovery having been met with.

(4) The Leishman-Donovan parasite was found in the peripheral blood in 86·6 per cent. of the cases.

(5) The ordinary grey monkey of the Sudan (*Cercopithecus sabœus*) can be infected with kala-azar.

(6) It can be infected by intraperitoneal inoculation and by subcutaneous inoculation.

(7) Natural infection, from an infected to a healthy animal, can occur provided the animals are kept in close contact.

(8) The Leishman-Donovan parasite is present in the peripheral blood of infected monkeys.

(9) So far we have found that the best method of infecting the monkey is by injecting into the peritoneal cavity the contents of a spleen puncture taken during life.

(10) So far we have not succeeded in infecting dogs, nor have we found spontaneous Leishmaniasis in the dog.

(11) The parasite can be cultivated readily on artificial media, development into flagellate forms being obtained in 10 per cent. citrate, on Novy and MacNeal's medium and on Nicolle's modification of that medium.

(12) The parasite appears to degenerate quickly after the death of the host. Post mortem examinations and post mortem spleen punctures for diagnostic purposes should be done immediately after death.

A paper by Visentini [1] is of special interest, because in it he traces and illustrates by a good coloured plate two modes of development of the parasite. In one there is a process of fission, two *Leishmania* being produced from one by division of the nucleus in the first instance and then of the blepharoplast. In the other, one finds a regular rosette formation. Balfour and Archibald [2] found similar appearances in splenic smears from a severe case treated by injections of "606." The drug appeared to cause some degeneration of the parasites, as evidenced by chromatolysis of their nuclei. Nicolle and Conor,[3] however, have succeeded in banishing the parasite from the blood and organs of infected monkeys by the use of the Ehrlich-Hata preparation, but unfortunately Nicolle, Cortesi, and Lévy [4] were not successful in the case of infantile kala-azar in children, albeit the salvarsan appeared in one case to cause degeneration of the *Leishmania*. It is difficult to make sure of the precise action of a drug in this disease, for most cases improve naturally every now and then, while a certain percentage undoubtedly recover. Recently Nicolle and Lévy [5] record a case of the infantile form in Tunis in a Jewish infant which terminated in complete recovery, the only one of twenty-five cases in which this has occurred. They do not think the benzoate of soda and anilin salt of antimony employed had anything to do with this fortunate termination. The amelioration of the symptoms and the return of the spleen to its normal size preceded the disappearance of the parasites.

The use of senega, advocated by Ensor,[6] undoubtedly seems to benefit certain cases of splenomegaly, and though one cannot definitely say it has ever cured a case of undoubted kala-azar, it seems worthy of a trial. Its virtues are supposed to depend on the saponin it contains, and as more of the latter is found in *Quillaia saponaria* (soap bark) of the U. S. P., Ensor suggests its use in preference to senega. The latter appears capable of producing a leucocytosis on which, possibly, some of its beneficial action depends. Quinine has long been used in the treatment of kala-azar, and finds a strong advocate in Muir,[7] who has had large experience in India, and believes if it is given hypodermically, and if cases are treated with it, early recovery is the rule.

The treatment consists of the injection of the following solution :—

Quin. sulphat.	Grains 32
Acid. sulph. dilut.	Drachm 1
Aqua distil.	Drachms 4

From 20 to 90 minims of this solution are injected into the latissimus dorsi muscle in adults, or into the gluteal region in children.

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[1] Visentini, A. (July, 1910), "Über die Morphologie und den Entwicklungskreis der bei Kranken Kalabriens und Siziliens beobachteten Leishmania." *Arch. f. Schiffs-u. Tropen-Hyg.*, Beiheft, Vol. XIV., No. 4.

[2] Balfour, A., and Archibald, R. G. (1911), "A case of Kala-azar treated by 606." *Fourth Report, Wellcome Tropical Research Laboratories*, Vol. A.

[3] Nicolle, C., and Conor, A. (December 14, 1910), "Application du 606 au traitement du Kala-azar." *Bull. Soc. Path. Exot.*

[4] Nicolle, C., Cortesi, A., and Lévy, E. (April 12, 1911), "Application de l'arséno-benzol au traitement du Kala-azar de l'enfant." *Ibid.*

[5] Nicolle, C., and Lévy, E. (March 8, 1911), "Un cas de Kala-azar terminé par la guérison." *Ibid.*

[6] Ensor, H. (December, 1909), "The treatment of Kala-azar by the use of Senega." *Journal Royal Army Medical Corps.*

[7] Muir, E. (February, 1911), "Treatment of Kala-azar by the Hypodermic Injection of a solution of Quinine Sulphate." *Indian Medical Gazette.*

Leishmaniasis—*continued*

The injection of such a solution is necessarily very painful, and where, as is generally the case, it has to be given repeatedly the patient naturally objects to it. The injection may be given absolutely painlessly, however, by a very simple expedient. Five minims of a 2 per cent. solution of cocaine is first injected; the needle is left inserted; the syringe withdrawn from it; the solution drawn up into it and injected after a couple of minutes into exactly the same place where the cocaine solution was injected.

The result of the injection, if given in the right dose, is to produce a certain amount of painless effusion, which lasts for a greater or less time depending on the dose and on the individual. If the blood be examined and a differential leucocyte count taken, a marked increase of the polymorphonuclear leucocytes will be noticed. In one case in which I had failed after searching three slides to find a single polymorph, I found 47 per cent. a week after such an injection. At the same time there is a very marked reduction in the size of the spleen and, if it is enlarged, in the size of the liver. As a rule, if the case is not very far advanced, the temperature becomes normal and, what is even more important, the patient begins to put on weight.

Injections have to be repeated as soon as, or rather before, the effusion from the first injection has disappeared, until the spleen and liver have entirely disappeared (*sic*). If too large a dose be given a certain amount of pain may accompany the effusion; but there will be a still greater leucocytosis, a still more rapid diminution in the size of the liver and spleen, and, although there may first be a few days' rise in temperature before it becomes normal, the appetite, weight and general health of the patient increase more rapidly.

He evidently regards the local irritation of the tissues at the site of injection as having a good deal to do with the result, for benefit is likewise obtained by turpentine injections which, however, are more painful. This, however, cannot be the only action, as he believes in giving cinchona by the mouth at the same time, finding it more effective than quinine. As a rule he administers a mixture of cinchona, arsenic, iron and magnesium sulphate while giving the injections, the amount of quinine administered being regulated by the effusion produced. He points out that kala-azar may be cured by the occurrence of cancrum oris, and cites the following interesting case :—

A patient was admitted to hospital with a large spleen extending to beyond the umbilicus and suffering from gangrene of the lung. He was coughing up large quantities of putrid matter by the mouth. The chest was drained by removing a part of a rib. The boy made a rapid recovery, but as long as there was any pus in his chest his spleen continued to diminish in size and the temperature remained normal. When, however, the wound in his chest had healed up there was a return of temperature accompanied by enlargement of the spleen. It was not till after three or four quinine sulphate injections that his temperature became normal and his spleen finally impalpable under the costal margin.

Muir's method is interesting when one recalls successful results in typhus fever by turpentine injections (*page* 389). This quinine or irritation therapy evidently demands a more extended use.

Additional Note

A useful recent paper on infantile Leishmaniasis,[1] illustrated by a coloured plate and giving prominence to the occurrence of chromatin granules in the tissues, is that by Jemma and Di Christina. It is in the main a review of recent work, and is furnished with a lengthy bibliography which will be found valuable by all interested in the subject.

Leprosy. Papers of bacteriological interest first claim attention. Smith and Bisset[2] deal with the subject chiefly from an historical aspect. They mention that Babes found leprosy bacilli to be slightly motile, and claimed to have seen branching forms in culture. They also quote Lehmann and Neumann as to the difference between tubercle and leprosy bacilli, the latter being more abundant, and appearing in heaps like a cigar in form, while the former are less numerous, and occur either singly or in irregular bunches. After staining, the granules in bacilli lepræ are coarse and widely separated, and in tubercle bacilli fine and close together. One point may be quoted as follows :—

They (leprosy bacilli) resist decoloration by acids, but to a less extent, according to Muir, Ritchie, and Woodhead, than do tubercle. Macé, however, states that they resist acids better than tubercle. Our own observations upon this point show that while tubercle bacilli appear red after 24 hours' immersion in 25 per cent. sulphuric acid, leprosy bacilli, which at the end of each hour up to 16 hours remain well stained, lose their stain after 18 hours' treatment; they are thus, according to Coles' table, more resistant to acids than all acid-fast bacilli except tubercle in sputum. The method we adopted was to place on the same slides smears of both bacilli, to ensure that in each case they received the same treatment.

The two bacilli were also similarly compared by Honsell's method, namely, after staining, washing and drying, by immersing for certain periods in a 3 per cent. solution of hydrochloric acid in alcohol, and then counterstaining in a saturated alcoholic solution of methylene blue. Up to 12 hours the tubercle bacilli retain their stain; after 2 hours the lepra bacilli remained well stained; after 3 hours very few could be distinguished, and after 6 hours

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[1] Jemma, R., and Di Christina, G. (June 24, 1911) "Über die Leishmania-Anämie der Kinder." *Cent. f. Bakt.*, I. Orig., Vol. LIX., No. 2.

[2] Smith, F. A., and Bisset, E. (1909), "The Bacteriology and Treatment of Leprosy." *Transactions Bombay Medical Congress.*

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